Request for permission for pharmaceutical industry oral testimony at Idaho Medicaid's P&T Committee meeting on 5-20-2016.

Submission # 6

As of May 9, 2016, this submission has not been accepted for oral presentation at the meeting.

Gennrich, Jane - Medicaid

From: noreply@salesforce.com on behalf of BMS Medical Information <bmsmedinfodonotreply@bms.com>
Sent: Friday, April 29, 2016 5:09 AM
To: Eide, Tamara J. - Medicaid
Cc: christopher.conner@bms.com
Subject: Response to your ELIQUIS® (apixaban) Request from Bristol-Myers Squibb Medical Information
Attachments: Fulfillment for Interaction - Eliquis Package Insert September 2015.pdf; Fulfillment for Interaction - BMS_00217044.pdf

Dear Dr. Tami Eide,

Thank you for contacting Bristol-Myers Squibb. Attached is the information you requested: - the Eliquis Medicaid Summary for the Indiana Medicaid P& T committee Meeting.

To respond to this message click here: Drug.information@bms.com

In case you receive this documentation in a HTML format please be aware that the attached files will be unavailable after 30 days. The data in this documentation is subject to change, please contact Medical Information for future queries on this topic.

Regards,
BMS Medical Information
Phone: 1-800-321-1335

Bristol-Myers Squibb

Dr. Tami Eide
Idaho Medicaid
3232 Elder Street
Boise, ID 83705

April 29, 2016

Dear Dr. Tami Eide,

Thank you for contacting Medical information about Eliquis® (apixaban). You have requested information regarding the Eliquis Medicaid Summary for the upcoming P& T committee Meeting.

ELIQUIS® (apixaban) is indicated:
– to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
– for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery
– for the treatment of DVT
– for the treatment of PE
– to reduce the risk of recurrent DVT and PE following initial therapy

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA
(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS **Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [*see Dosage and Administration (2.4) and Warnings and Precautions (5.1), and Clinical Studies (14.1)]***
(B) SPINAL/EPIDURAL HEMATOMA **Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:**
• use of indwelling epidural catheters **• concomitant use of other drugs that affect hemostasis, such as nonsteroidal antiinflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants** **• a history of traumatic or repeated epidural or spinal punctures** **• a history of spinal deformity or spinal surgery** **• optimal timing between the administration of ELIQUIS and neuraxial procedures is not known** ***[see Warnings and Precautions (5.3)]*.**
Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary. *[see Warnings and Precautions (5.3)].* **Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated*[see Warnings and Precautions (5.3)]***

Summary:

Apixaban-HEOR-Medicaid Summary-3 pages-ID-APR16

Please note that Bristol-Myers Squibb does not recommend the use of ELIQUIS in any manner inconsistent with that described in the full prescribing information. Please consult the Full Prescribing Information for ELIQUIS, including **Boxed WARNINGS regarding (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS** and **(B) SPINAL/EPIDURAL HEMATOMA.**

Please refer to the end of this information packet for the following:

- Reporting adverse event cases or product quality complaints, or to provide information on exposure to a BMS product during pregnancy or lactation.

- Alliance to develop and commercialize Eliquis.

With the aim to continuously improve the quality of our service we would like to request you complete a brief satisfaction survey. It will only take you 3 minutes to complete. The survey can be accessed at the below link: https://service7.soundbite.com/site/c/3000164472/csat/?caseid=500o000000E2ALJ&fulid=a39o00000005WWq

We trust that you will find this information helpful. If you have further questions or require additional information, please contact BMS Medical Information Department at 1-800-321-1335.

Sincerely,
BMS Medical Information

Enclosures:
Eliquis Package Insert September 2015.pdf.

ELIQUIS® (Apixaban) 2.5 and 5 mg Tablets
Idaho Medicaid Summary

COVER SHEET

Attention Idaho Medical Reviewer:
Please find enclosed the ELIQUIS® Medicaid Summary prepared for the Idaho Medicaid meeting on May 20, 2016. This information is provided as a professional courtesy in response to a request forwarded by Christopher Conner, PharmD, PhD, US Field HEOR Scientist, Bristol-Myers Squibb Company.

ELIQUIS®

- NEW STUDIES:
  - A meta-analysis of randomized clinical trials to compare the efficacy and safety outcomes of newer oral anticoagulants (NOACs) compared with warfarin in patients with nonvalvular atrial fibrillation (NVAF) (page 1; STUDY 1). This analysis suggested that apixaban was the only NOAC associated with significant reduction in risk of stroke or SE and major bleeding vs. warfarin in patients with NVAF.
  - A real-world retrospective database analysis designed to evaluate the hospital readmission rates in patients with NVAF who were prescribed direct oral anticoagulants (page 2; STUDY 2). This analysis suggested that, relative to NVAF patients prescribed apixaban, the odds of all cause and bleeding related 1-month hospital readmissions were higher for rivaroxaban.
  - A real-world retrospective database analysis designed to evaluate the hospital length of stay and associated costs in patients with NVAF (page 2; STUDY 3). This analysis suggested that, relative to patients prescribed apixaban, patients prescribed warfarin experienced longer hospital LOS and higher associated hospitalization costs.
  - A summary of two meta-analyses of randomized clinical trials to compare the efficacy and safety outcomes of NOACs for the extended treatment of VTE (page 2; STUDY 4).

No adequate and well-controlled head-to-head clinical trials have been conducted comparing the efficacy and safety of Apixaban vs. Rivaroxaban, Dabigatran or Edoxaban. The meta-analyses and real-world retrospective database analyses evaluating novel oral anticoagulants do not imply comparable efficacy, safety, or product interchangeability. Interpretation of results is based on statistical association not causality.

The purpose of this document is to provide available scientific information regarding Eliquis as requested by the Idaho State Medicaid Meeting; it is not intended to be used for any other purpose. This document contains relevant information for Eliquis, which may or may not be included in the U.S. Prescribing Information (USPI). BMS/Pfizer do not suggest or recommend the use of Eliquis in any manner other than as described in the USPI.

ELIQUIS® (Apixaban) 2.5 and 5 mg Tablets
Factor Xa Inhibitor Anticoagulant

Idaho Medicaid Summary

Indications	Recommended Dosage[a,b,c,1]
Reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF)	• 5 mg orally twice daily • In patients with ≥2 of the following characteristics (age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL): 2.5 mg orally twice daily
Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery	• 2.5 mg orally twice daily
Treatment of DVT and PE	• 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily
Reduction in the risk of recurrent DVT and PE following initial therapy	• 2.5 mg taken orally twice daily

[a] Eliquis can be taken with or without food. [b] Coadministration with strong dual CYP3A4 and P-gp inhibitors: For patients receiving eliquis doses greater than 2.5 mg twice daily, reduce the dose by 50% when eliquis is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of eliquis with strong dual inhibitors of CYP3A4 and P-gp. [c]No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except NVAF patients who meet the criteria for dosage adjustment. Patients with ESRD (CrCl < 15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with eliquis; therefore the dosing recommendation are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subject with ESRD maintained on dialysis.

No adequate and well-controlled head-to-head clinical trials have been conducted comparing the efficacy and safety of Apixban (Apix) vs. Rivaroxaban (Riva)/Dabigatran (Dabi)/Edoxaban (Edox) for reducing the risk of stroke or systemic embolism in patients with NVAF. The meta-analyses and real-world retrospective database analyses evaluating novel oral anticoagulants do not imply comparable efficacy, safety, or product interchangeability. Interpretation of results is based on statistical association not causality.

REDUCTION OF RISK OF STROKE AND SYSTEMIC EMBOLISM IN NVAF

STUDY 1. A Meta-analysis of Randomized Clinical Trials

The findings of a meta-analysis of four pivotal phase 3, randomized clinical studies RE-LY[2], ROCKET-AF[3], ARISTOTLE[4], and ENGAGE AF-TIMI 48[5] that compared the risk of stroke or systemic embolism (SE), and major bleeding events for the novel oral anticoagulants (NOACs), apixaban (Apix), rivaroxaban (Riva), dabigatran (Dabi), and/or edoxaban (Edox), vs. Warfarin (Warf) in NVAF patients (N = 71,683) are summarized in Table 1. The results of this meta-analysis showed that only Apix was associated with significant reduction in risk of stroke and SE and less major bleeding vs. Warf.[6]

Table 1: Stroke, Systemic Embolic or Major Bleeding Events

	ARISTOTLE Apix vs Warf RR (95% CI)	RE-LY Dabi vs Warf	ROCKET-AF Riva vs Warf	ENGAGE AF-TIMI 48 Edox vs Warf	Pooled[1]
Stroke or Systemic Embolism[2]	0.80 (0.67-0.95)	0.66 (0.53-0.82)	0.88 (0.75-1.03)	0.88 (0.75-1.02)	0.81 (0.73-0.91)
P value	**.012**	**.0001**	.12	.10	<.0001
Major bleeding[3]	0.71 (0.61-0.81)	0.94 (0.82-1.07)	1.03 (0.90-1.18)	0.80 (0.71-0.90)	0.86 (73-1.00)
P value	**<.0001**	.34	.72	**.0002**	.06

RR, Risk Ratio [1]Data from RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials. Only high dose data from RE-LY and ENGAGE AF were included in the analysis. [2]Heterogeneity: $I^2 = 47\%$, $P = .13$. [3]Heterogeneity: $I^2 = 83\%$, $P = .001$

STUDY 2. Using the Premier Hospital Database, a retrospective, observational cohort study evaluated 1-month readmissions and related hospital costs from 01JAN2012 - 28FEB2014 among adult NVAF patients prescribed Apix (n = 4,138), Dabi (n = 32,838), or Riva (n = 37,754). At baseline, Apix patients were older (Apix: 73.6 years vs. Riva: 72.3 years, vs. Dabi: 71.9 years, $P < .0001$) and had higher risks of stroke and bleeding as measured by $CHADS_2$ (Apix: 2.19 vs. Riva: 2.04 vs. Dabi: 2.09, $P < .0001$) and HAS-BLED scores (Apix: 2.56 vs. Riva: 2.35 vs. Dabi: 2.33, $P < .0001$). After adjusting for baseline characteristics, when compared to Apix, the odds of all cause and bleeding related 1-month hospital readmissions were statistically significant higher for Riva (OR: 1.2, 95% CI 1.1-1.3, $P < .001$ and OR: 1.4, 95% CI 1.1-1.8, $P < .01$, respectively), and not statistically significant higher (OR:1.1, 95% CI 1.0-1.2, $P = .21$, ns, and OR: 1.2, 95% CI 0.9-1.6; $P = .16$, ns, respectively) for Dabi. When compared to Apix, the use of Riva was associated with statistically significant longer hospital lengths of stay (LOS) of 0.25 days ($P < .001$) and the use of Dabi was associated with not statistically significant longer LOS of 0.11 days ($P = .10$, ns), for the 1-month readmissions. When compared to Riva, Apix had a statistically significantly lower mean all-cause hospital costs per patient of $413 (95% CI: $142-$684; $P = .003$) for 1-month readmissions. When compared to Dabi, Apix had a numerically lower but not statistically significant mean all-cause hospital costs per patient of $142 (95% CI: –$132 to $417; $P = .31$, ns).

- Limitations included: database contained information from a large number of U.S. hospitals, which may not be representative of the entire U.S. population of NVAF patients; billing and coding errors and missing data may have occurred.[7]

STUDY 3. Using the Premier Perspective Claims Database, a retrospective, observational cohort study evaluated hospital length of stay (LOS) and costs among NVAF patients prescribed Apix (n = 2,894) or warfarin (n = 124,174). Adult patients hospitalized with AF were selected from the Premier Perspective Claims Database (01JAN2013-31MARCH2014). Patients with evidence of valvular heart disease, valve replacement procedures, or pregnancy during the index hospitalization were excluded. Propensity score matching (PSM) was performed to control for baseline imbalances between patients prescribed with Apix or warfarin. Patients prescribed warfarin were older and sicker compared to those treated with Apix at baseline. After applying PSM, a total of 2,886 patients were included in each cohort, and baseline characteristics were balanced. The mean (standard deviation [SD] and median) hospital LOS was significantly ($P = .002$) shorter for patients prescribed Apix 5.1 days (5.7 and 3.0) compared to warfarin 5.5 days (4.8 and 4.0). Patients prescribed Apix incurred significantly lower hospitalization costs compared to those prescribed warfarin ($11,262 vs. $12,883; $P < 0.001$).

- Limitations included: propensity score methods do not address confounding in unobserved characteristics such as unmeasured health status and socioeconomic status; other measures, such as AF duration, pre-index oral anticoagulation use, over-the-counter medication use and patient health behavior could not be measured; as is the case for claim-based studies, there may be coding errors or diagnoses entered for administrative processing rather than clinical completeness; Baseline characteristics were captured 12 months prior to the index hospitalization based on hospital information only. Therefore, the patient comorbidity indices and conditions may be underestimated; database contained information from a large number of hospitals, which may not be generalizable to the entire U.S. population of NVAF patients; the Premier Hospital Database represents only hospital costs and does not represent care received outside a hospital facility.[8]

TREATMENT OF DVT AND PE, AND FOR THE REDUCTION IN THE RISK OF RECURRENT DVT AND PE, FOLLOWING INITIAL THERAPY

STUDY 4. Meta-analyses of Randomized Clinical Trials

The findings of two meta-analyses[9],[10] of the phase 3, randomized clinical trials RE-SONATE[11], EINSTEIN-EXT[12], and AMPLIFY-EXT[13] to compare the efficacy and safety of NOACs (Apix, Riva, Dabi) vs. placebo for the reducing the risk of recurrent DVT and PE are summarized in Table 2.

Table 2: Recurrent VTE and Major or CRNM Bleeding Events[9,10]

	AMPLIFY-EXT Apix vs. Placebo	RE-SONATE Dabi vs. Placebo	EINSTEIN-EXT Riva vs. Placebo	Total Events
VTE Recurrence				
Kakkos 2014, RR (95% CI)	0.19 (0.13-0.30)	0.08 (0.03-0.26)	0.19 (0.09-0.40)	**0.17 (0.12-0.24)**
Sarddar 2013, OR (95% CI)	0.18 (0.11-0.28)	0.07 (0.02-0.24)	0.18 (0.08-0.38)	**0.16 (0.11-0.24)**
Major or CRNM Bleeding				
Kakkos 2014, RR (95% CI)	1.41 (0.88-2.28)	2.92 (1.53-5.56)	5.07 (2.28-11.31)	**2.61 (1.24-5.49)**
Sarddar 2013, OR (95% CI)	1.43 (0.87-2.34)	3.00 (1.54-5.81)	5.34 (2.35-12.09)	**2.69 (1.25-5.77)**

CRNM, clinically relevant non-major; RR, risk ratio, OR, odds ratio

Selected Important Safety Information

WARNINGS: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

Contraindications: Active pathological bleeding, Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions).

Please see attached full Prescribing Information, including boxed warnings accompanying this document and available at the presentation.

REFERENCES:

1 Eliquis (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ and Pfizer Inc, New York, NY
2.Connolly S, et al. Dabigatran vs warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-1151.
3. Patel MR, et al. Rivaroxaban vs warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;385(10):883-891.
4. Granger C, et al. Apixaban vs warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-992.
5. Giugliano R, et al. Edoxaban vs warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093-2104
6. Ruff C, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955-962.
7. Deitelzweig S, J et al. An early evaluation of bleeding-related hospital readmissions among hospitalized patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants. *Curr Med Res Opin.* 2016; 32(3):573-82.
8. Xie L et al. Comparison of hospital length of stay and hospitalization costs among patients with non-valvular atrial fibrillation treated with apixaban or warfarin: an early view. *J Med Econ.* 2016 Mar 30:1-25.
9. Kakkos SK, et al. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg.*2014;48(5):565-575.
10. Sardar P, et al. Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials. *Drugs.* 2013;73:1171-1182.
11. Schulman S, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med.* 2013;368:709-718.
12. Bauersachs R, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363:2499-2510.
13. Agnelli G, et al. Apixaban for extended treatment of venous thromboembolism. *N Eng J Med.* 2013;368:699-708.

For Your Consideration:

Adverse Event / Pregnancy

If you become aware of a patient who has experienced an adverse event with a BMS product, has received treatment with a BMS product during pregnancy or lactation, or has become pregnant while her partner received treatment with a BMS product, please contact us at 1-800-721-5072.

Alliance Statement

Bristol-Myers Squibb and Pfizer have formed an Alliance to develop and commercialize Eliquis. The Alliance parties have agreed that Bristol-Myers Squibb shall respond to all unsolicited requests for medical information on Eliquis (apixaban).

Bristol-Myers Squibb